



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Ulf TILSTAM et al.

Group Art Unit: 1623

Serial No.: 09/471,040 :

Examiner: Elli PESELEV

Filed: December 23, 1999 :

For: PROCESS FOR THE PRODUCTION OF FLUDARABINE-PHOSPHATE LITHIUM,  
SODIUM, POTASSIUM, CALCIUM AND MAGNESIUM SALTS AND  
PURIFICATION PROCESS FOR THE PRODUCTION OF FLUDARABINE-  
PHOSPHATE AND FLUDARABINE-PHOSPHATE WITH A PURITY OF AT LEAST  
99.5%

**DECLARATION UNDER 37 C.F.R. § 1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Harald Rabe being duly warned, declares that:

I am the same Harald Rabe who filed the previous Declaration Under 37 C.F.R. § 1.132,  
which was executed by me on February 23, 2006.

In that Declaration, data were presented regarding the level of impurities in the crystalline solid obtainable via the process described in the document referred to as "OD29." These were shown to be greater than that permitted by the claims of this application; i.e., the impurity level was greater than 0.5% in the crystalline fludarabine phosphate produced by the process of OD29.

I repeat below the objection which the examiner has regarding the sufficiency of these data to establish the fact that the OD29 process cannot produce fludarabine phosphate of a purity equal to or greater than 99.5%:

The declaration states that “a highly pure fludarabine phosphate could be obtained in a liquid solution” having purity of more than 99.5%. Applicant contends that when the prior art crystals were reconstituted in water, the purity was less than 99.5%. However, the declaration fails to show that the purity of prior art crystals before reconstitution with water is substantially less than [sic] 99.5%. Therefore, the above stated rejection has not been overcome.

In other words, the examiner refers to the fact that the crystals per se obtained using the process of OD29 were not measured for impurities, i.e., in the crystalline state. Rather, their impurity level was established after they were reconstituted in water (as also described in OD29).

Although the examiner’s question is understandable, the definitive fact is that the data in the prior declaration do establish that the crystals themselves produced by the OD29 process contain impurity levels greater than those permitted, i.e., greater than 0.5%, i.e., provide fludarabine phosphate crystals of a purity less than 99.5%.

Firstly, the reason the crystals themselves were not analyzed was that normal, sophisticated laboratory instruments are not capable of measuring very low amounts of impurities such as those listed in Table IV of the prior declaration. In any event, as explained below, measurements performed on the crystals themselves are not necessary to establish firmly that the crystals themselves contain impurity levels greater than permitted by the patent claims of the above-identified application.

Underlying the examiner’s point, no doubt, is the fact that it has been established of record that fludarabine phosphate decomposes in aqueous solution at various rates depending on temperature, humidity, pH, time, etc. See the Test Report (Experiment 6) attached to the prior declaration.

As stated in the prior declaration, our experiments reproduced the methods of OD29 as closely as possible (page 5, line 20). These included preparation of the crystalline solid at room temperature under vacuum and subsequent reconstitution in water for injection (page 5, lines 12-14). All of our OD29-related experiments were performed at room temperature, as would be the norm for the methods described in OD29, including the particular step at issue by the examiner, i.e., reconstitution with water followed by impurity determination.

As shown in the mentioned Test Report (Experiment 6), for a test solution having 0.91% of impurities at 25° C, after thirty days at a temperature 50° C, the amount of impurities increases to 1.10%. See the table at the bottom of the second page of the Test Report (Experiment 6). (Other temperature data are also given, e.g., at 60°, 70°, 80°, etc. These show, overall, somewhat elevated degrees of decomposition. The following discussion is based on the 50° decomposition results since these come closest to room temperature and still provide a worst case scenario in answering the examiner's question.) Thus, at 50° C, on average, the amount of contaminants increases at the rate of 0.7% per day ( $1.10 - 0.91 / 0.91 \div 30$ ).

In all of our experiments, after the crystals were reconstituted in water for injection, the impurity levels were always measured well within one day. These crystals had an impurity content of 0.33% at the outset. See Table IV, Row 2 of the prior declaration. Thus, given the 50° average daily decomposition rate, the maximum amount of contamination which could be contributed by decomposition of fludarabine phosphate over a whole day would be 0.33% + 0.0063% (the beginning contamination degree times the percent decomposition for one day based on the 50° data), for a total contamination of 0.3363%. However, under all tested conditions, the minimum degree of total contamination was very much higher, i.e., 1.48%. This is many orders

of magnitude greater than the contamination which could be contributed by decomposition of fludarabine phosphate due to the reconstitution conditions. Thus, the source of such large degrees of contamination has to be the original crystalline solid itself used for the reconstitution process. In other words, our experiments provided proof that the solids themselves contained the very large amounts of impurities shown in the last column in Table IV of the prior declaration.

Thus, even based on a worst case scenario of 50° C (rather than the room temperature conditions which were actually used in the experiments), the maximum contribution to contamination of the crystalline solid which could be caused by decomposition of fludarabine phosphate during reconstitution is very much lower than that required to arrive at the actually measured contamination levels. Unambiguously, the latter reflect the impurity content of the starting material crystalline solid fludarabine phosphate itself for all experiments.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

8.12.06  
Date

Dr. Harald Rabe  
Harald Rabe